

**REMARKS**

Claims 2-16 and 19-22 are pending after entry of this paper. Claims 2-8 and 21 have been rejected. Claims 9-16, 19-20 and 22 have been withdrawn and claims 1 and 17-18 have been cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a continuing application. Claims 2, 4 and 6 have been amended.

Claim 2 has been amended to partially incorporate the subject matter of claim 4. Support may be found throughout the instant specification and previously presented claims, for example, claim 4.

Claim 4 has been amended to delete the phrase “osteoblasts, skeletal myoblasts, chondrocytes or.”

Claim 6 has been amended to replace the term “nerve” with the term “neurons” based on the Examiner’s suggestion (Office Action – page 3).

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

**Response to Rejections under 35 U.S.C. §102**

Claims 1-8 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zhao, et al. (*PNAS*, 100: 2426-2431, 2003). Specifically, the Examiner contends that Zhao allegedly discloses the isolation of pluripotent stem cells (PSC) from human peripheral blood monocytes that resemble fibroblasts and express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45, and the presence of collagen

type I would be inherent (Office Action – page 4). Moreover, according to the Examiner, Zhao further discloses that human peripheral blood cells containing monocytes when cultured under specific conditions, differentiate into macrophages, lymphocytes, epithelial cells, neuronal cells, endothelial cells and hepatocytes (Office Action – page 5). Therefore, the Examiner maintains that Zhao allegedly anticipates the claimed invention and the burden to prove that inherency is not involved falls on the applicants (Office Action – page 6). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 2 to partially incorporate the subject matter of claim 4 by reciting “wherein the cell is able to differentiate into osteoblasts, skeletal myoblasts or chondrocytes.” In addition, applicants submit herewith a declaration under 37 CFR §1.132 by Dr. Masataka Kuwana (one of the inventors). The declaration discloses:

- (1) results of experiments to culture MOMC under the differentiation induction conditions of PSC (paragraph 7), and
- (2) results of check-up experiments of the method of Zhao, et al. (paragraph 8) are described.

The results of experiments (1) clearly show that MOMCs cultured under the differentiation induction conditions of Zhao, et al. do not differentiate into neuronal cells, epithelial cells or hepatocytes. On the other hand, PSC under the conditions of Zhao et al. as described are able to differentiate into neuronal cells, epithelial cells or hepatocytes. Thus, one skilled in the art would not and could not consider that MOMCs of the instant invention are the same as the PSCs of Zhao, et al.

Furthermore, as described in the enclosed declaration, Dr. Kuwana attempted to prepare PSCs with the method disclosed by Zhao, et al. However, the resultant “cells morphologically resembling fibroblasts” do not show all of the characteristics described in the

Zhao, et al. reference, which itself casts doubt on the reproducibility of the method of Zhao, et al. Moreover, these “cells morphologically resembling fibroblasts” prepared by the method of Zhao, et al. do not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation induction conditions of MOMC set forth in the instant application (see Example 22 of the specification). Therefore, these results would imply to one skilled in the art that PSCs of Zhao, et al. are unable to differentiate into osteoblasts, skeletal myoblasts or chondrocytes.

In light of these experimental results, inventor’s declaration and amendments to claims, applicants respectfully assert that PSCs are unable to differentiate into “osteoblasts, skeletal myoblasts or chondrocytes” as experimentally confirmed and the ability to differentiate into these cells can not be asserted to be inherent as suggested by the Examiner. Furthermore, MOMCs cultured under the differentiation induction conditions of Zhao, et al. as discussed above do not differentiate into neuronal cells, epithelial cells or hepatocytes, whereas, PSCs do. Hence, MOMC currently claimed in the instant invention is not anticipated by PSC of Zhao, et al. expressly or inherently because Zhao does not disclose each and every element of the claims as presented herewith. Reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) of claims 1-8 as being anticipated by Zhao, et al. are respectfully requested.

#### Response to Rejections under 35 U.S.C. §103

Claim 21 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Zhao, et al. (*PNAS* 100: 2426-2431, 2003) in view of Pujol, et al. (*Differentiation* 65: 287-300, 2000). Specifically, the Examiner contends that Zhao allegedly discloses the pluripotent stem cells expressing CD14, CD34 and CD45 that are obtained by culturing peripheral blood mononuclear cells. The Examiner attempts to reach the claimed invention by combining the

teachings of Zhao, et al. and Pujol, et al. According to the Examiner, Pujol allegedly teaches culturing CD14 monocytes derived from PBMC on fibronectin-coated tissue culture plates (page 288, “Cell Culture”) and one skilled in the art would be motivated to combine the teachings from the two publications to arrive at the claimed invention disclosed in claim 21. Applicants respectfully disagree.

Applicants assert that contrary to the Examiner’s contention, Zhao does not disclose MOMC of the instant invention as presented in the arguments above. Therefore, neither the combination of, nor Zhao, et al. and Pujol, et al. alone, suggests the claimed elements such as the monocyte-derived multipotent cells (MOMC). Pujol does not remedy the deficiencies in the monocyte derived cells (PSC) of Zhao, et al. Therefore, the combination of Zhao, et al. and Pujol, et al. does not make obvious the claimed invention. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection of claim 21 in view of the aforementioned remarks and amendments to the claims.

#### Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim 2 from which all of the dependent claims 3-8 and 21 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

### **CONCLUSION**

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

**AUTHORIZATION**

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4036.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4036.

Respectfully submitted,  
MORGAN & FINNEGAN, L.L.P.

By: 

Evelyn M. Kwon  
Registration No. 54,246

Dated: October 10, 2007

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s): Masataka KUWANA, et al.

Group Art Unit: 1649

Serial No.: 10/549,707

Examiner: Dutt, Aditi

Filed: October 27, 2005

Confirmation: 2198

For: MONOCYTE-ORIGIN MULTIPOTENT CELL MOMC

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This is a Declaration under 37 C.F.R. §1.132 by Masataka Kuwana, MD, Ph.D. in the above-identified application.

I, the undersigned, Masataka Kuwana, declare and state that:

1. I am a co-inventor of the subject patent application having serial no. 10/549,707.
2. My education and professional experience as an expert in the area of tissue engineering are set forth on the attached copy of my Curriculum Vitae.

3. I have read and understand U.S. Patent Application Serial No. 10/549,707, entitled "MONOCYTE-ORIGIN MULTIPOTENT CELL MOMC," and I submit this Declaration in its support.

4. I have read and understand the August 10, 2007 Final Official Action issued in the above-identified case.

5. I have read and understand the publication of Zhao, et al. (*PNAS*, 100: 2426-2431, 2003) cited by the Examiner.

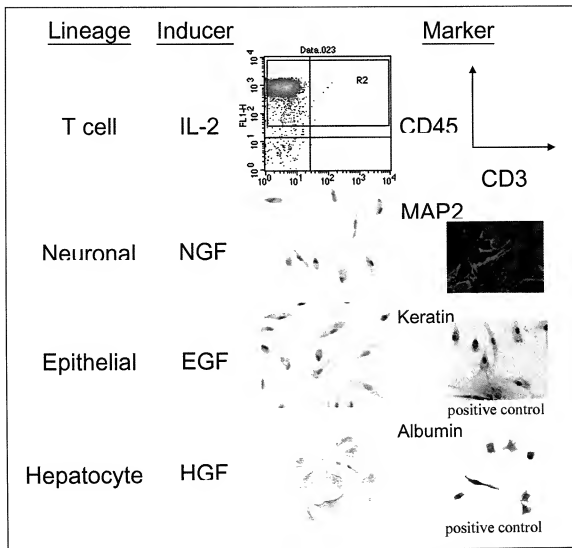
6. In particular, I understand that in the August 10, 2007 Final Official Action, the Examiner has rejected claims 2-8 because they are anticipated by Zhao, et al. Specifically, the Examiner states that the Zhao, et al. reference teaches the isolation of pluripotent stem cells (PSC) from human peripheral blood monocytes that resemble fibroblasts and express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45. The Zhao, et al. reference allegedly further discloses that human peripheral blood cells containing monocytes, when cultured under specific conditions, differentiate into macrophages, lymphocytes, epithelial, neuronal, endothelial and hepatocytes (Final Office Action- pages 3-6). As a person skilled in the art, I respectfully disagree with the Examiner's rejection.

7. The inventors of the instant application attempted the differentiation induction of MOMC into T-cells using IL-2, as described in Zhao, et al. The expression of CD3 was analyzed with a flow cytometry technique. The results, as shown in Figure 1 below, demonstrate that CD3 was not expressed. Thus, MOMC does not differentiate into T-cell using the method described in Zhao, et al.. Furthermore, the inventors attempted the differentiation induction of



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MOMC into neuronal cells, epithelial cells and hepatocytes using NGF, EGF and HGF, respectively. When MOMC was immunostained with an immunoenzymatic method, no brown coloration of MOMC was observed. As shown in Figure 1 below, MAP2 (a marker of neuronal cells), keratin (a marker of epithelial cells), and albumin (a marker of hepatocytes), were not expressed. Hence, it was shown that MOMC does not differentiate into neuronal cells, epithelial cells or hepatocytes. These results show that MOMC are clearly distinct from PSC.



**Figure 1:** Results of experiments concerning differentiation abilities of human MOMC cultured under the differentiation conditions of PSC into T-cells, neuronal cells, epithelial cells and hepatocytes.

8. Finally, the inventors have also carried out a check experiment, and the results of Zhao, et al. were not reproducible<sup>1</sup>. The steps of the check experiments carried out by the inventors are set forth here. Monocytes were cultured according to the method of Zhao, et

<sup>1</sup> Reproducibility is solely based on the disclosure of Zhao, et al. and does not mean that there is no reproducibility in Zhao, et al. when special techniques or materials are used but not disclosed in their article.

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al.(with medium containing M-CSF and LIF), and cells morphologically resembling fibroblasts were observed. However, the frequency of the "cells that morphologically resembled fibroblasts" was much lower than that described in Zhao, et al., and though their cloning was attempted through the method described in Zhao, et al, the cells did not proliferate and clone. The data, therefore, which should be obtained from their separation, purification and analysis were not available. Moreover, their flow cytometry analysis showed a slight expression of CD34 in the cells, which is within the margin of error of flow cytometry analysis. The expression of CD34 was not detected with either immunostaining or the RT-PCR method as shown in Zhao, et al. Furthermore, the inventors confirmed that the cells cultured according to the method of Zhao, et al., which include the "cells that morphologically resembled fibroblasts," did not express CD3 in the presence of IL-2, vWF in the presence of EGF, or AFP in the presence of HGF. These cells also did not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation induction conditions of MOMC set forth in the instant application.

9. Zhao et al. disclose pluripotent stem cells (PSC) which express CD14, CD34 and CD45. Zhao et al. also describe that PSC differentiate into macrophages, lymphocytes, epithelial cells, neuronal cells, endothelial cells and hepatocytes. However, the Monocyte-Origin Multipotent Cells (MOMC) of the instant invention are much different from PSC of Zhao et al. in their properties, especially their differentiation abilities as demonstrated in Table 1 below.

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TABLE 1.

	PSC	MOMC
Differentiation Abilities		
T-lymphocyte	+	-
epithelial cell	+	-
endothelial cell	+	+
neuronal cell	+	Culture under NGF stimulation (culture condition of PSC): - Coculture with rat neurons: +
hepatocyte	+	-
mesenchymal cell	not reported	+
proliferation from a single cell (cloning)	possible	impossible

The "+" and "-" signs show whether human MOMC cultured under the differentiation condition of PSC has a differentiation ability or not.

10. In view of the evidence presented above, there is a clear difference in differential abilities between MOMC and PSC. Furthermore, the cells of Zhao, et al. do not express vWF in the presence of EGF and do not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation induction conditions of MOMC. Therefore, one skilled in the art would conclude that MOMC is clearly distinct from said "cells that morphologically resembled fibroblasts" (Zhao, et al. page 2427, column 1, 3<sup>rd</sup> paragraph).

11. Thus, it is my experience and my opinion, as one skilled in the art of tissue engineering, that MOMC and PSC cells are not identical, in view of the differences in the differential abilities of these cells. These differences of differential abilities necessarily result in the differences of diseases for which these cells will be used as a transplant in the future. It is

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clear from these points that the instant invention could not be anticipated by the teachings of Zhao, et al.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Respectfully submitted,

Date : \_\_\_\_\_

  
Masataka Kuwana

July 1, 2007

## CURRICULUM VITAE

**NAME:**

Masataka Kuwana

**ACADEMIC TITLE:**

Associate Professor

**SEX:**

Male

**BIRTH DATE:**

May 16, 1963

**BIRTHPLACE:**

Tokyo, Japan

**CURRENT ADDRESS:**

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**EDUCATION:**

<u>Institution and Location</u>	<u>Degree</u>	<u>Year Conferred</u>	<u>Field of Study</u>
Keio University School of Medicine Tokyo, Japan	MD	May, 1988	Medicine
Keio University School of Medicine Tokyo, Japan	PhD	January, 1992	Cell biology Immunology

**BOARD CERTIFIED MEMBERS:**

1994	Board Certified Member of the Japanese Society of Internal Medicine
1995	Board Certified Member of the Japanese College of Rheumatology
1995	Fellow of the Japanese Society of Internal Medicine
2005	Instructor of the Japanese College of Rheumatology

**RESEARCH AND PROFESSIONAL EXPERIENCE:**

1988-1992	Graduate student, Keio University School of Medicine, Tokyo, Japan
1992-1993	Postdoctoral Fellow, Division of Rheumatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
1993-1996	Postdoctoral Research Fellow, Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

1996-1998	Instructor, Division of Rheumatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
1998-2000	Instructor, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan
2000-2005	Assistant Professor, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan
2006-Present	Associate Professor and Chief, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

# **AWARD:**

	<u>Source</u>	<u>Type of Support</u>
1993-1994	Arthritis Foundation, Western Pennsylvania Chapter	Research Fellowship Award
1995	American Clinical Research Meeting	Travel Award
1995	American College of Rheumatology	Senior Rheumatology Scholar Award
1998	Naito Foundation	Research Award
1999	Japanese Intractable Diseases Foundation	Research Prize
2000	Sakaguchi Research Foundation	Research Award
2001	Ichiro Kanehara Foundation	Research Prize
2001	Mochida Memorial Foundation	Research Award
2001	Uehara Life Science Foundation	Research Award
2002	Keio University School of Medicine Sanshikai	Yong Investigator Award
2002	Terumo Life Science Foundation	Research Award
2002	Nagao Memorial Fund	Research Prize
2003	Japan Rheumatism Association	Research Award
2004	Japanese Society for Connective Tissue Research	Otaka Memorial Prize
2005	Keio University Intellectual Program Center	Honorary Award
2005	Takeda Science Foundation	Research Award
2005	Keio University School of Medicine Sanshikai	Kitajima Memorial Prize
2007	International Systemic Sclerosis	Travel Award

	Forum 2007	
2007	Japan Rheumatism Foundation	Research Prize

**EDITORIAL BOARD:**

2001-2005	Editorial Board, Connective Tissue
2002-2005	Editorial Board, Japanese Journal of Clinical Immunology
2004-now	International Editor, Drugs
2005-now	Advisory Editor, Arthritis and Rheumatism
2006-now	Editorial Board, Journal of Infectious Diseases

**MEMBER:**

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 American Association of Immunologists  
 New York Academy of Science  
 Japanese Society of Internal Medicine  
 Japanese College of Rheumatology  
 Japanese Society for Immunology  
 Japan Society for Clinical Immunology  
 Japanese Society of Clinical Hematology  
 Japanese Society for Connective Tissue Research  
 Japanese Society for *Helicobacter* Research  
 Japanese Society of Inflammation and Regeneration



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10. Kuwana M, Kaburaki J, Okano Y, Tojo T, and Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Arthritis Rheum.* 1994; 37(1): 75-83.
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- gene polymorphisms in systemic sclerosis: interactive effect of MHC class II and KM genes on anticentromere antibody production. *Ann. Rheum. Dis.* 1998; 57(6): 366-370.
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